I concur with this review memo. B. Robinson 01/07/2016
I concur with this review. M. Serabian 01/07/16

FOOD AND DRUG ADMINISTRATION
Center for Biologics Evaluation and Research
Office of Cellular, Tissue, and Gene Therapies
Division of Clinical Evaluation and Pharmacology/Toxicology
Pharmacology/Toxicology Branch

BLA NUMBER:	STN#125585.000
DATE RECEIVED (BY DCC):	28-Jan-2015
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SPONSOR: Puget Sound Blood Center and Program Cord Blood Services

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PRODUCT NAME: Hematopoietic Progenitor Cells (HPC), Cord Blood
PRODUCT PROPRIETARY NAME: N/A

PROPOSED INDICATION: Allogeneic cord blood hematopoietic progenitor cell therapy indicated for use in unrelated donor hematopoietic progenitor cell transplantation procedures in conjunction with a preparative regimen appropriate for treatment of the patient's disease and for hematopoietic and immunologic reconstitution in patients with hematopoietic system-affecting diseases that are inherited, acquired, or result from chemotherapy and/or radiation intended to treat their disease.

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Formulation and Chemistry:

The product, HPC, Cord Blood, is a cellular biologic product containing human umbilical cord blood (CB) cells generated after volume reduction and partial red blood cell (RBC) and plasma depletion. The final cell suspension contains 10% dimethyl sulfoxide (DMSO) and 1% Dextran 40. This suspension is then cryopreserved at a controlled rate in liquid nitrogen ((b) (4). The

final product, HPC, Cord Blood, contains a minimum of 5 x 10^8 total nucleated cells (TNCs) with a minimum of 1.25 x 10^5 CD34+ cells and a post-processing viability of at least 85%.

Abbreviations:
BLA = Biologic License Application
CB = Cord Blood
CBU = Cord Blood Unit
DMSO = Dimethyl Sulfoxide
GVHD = Graft Versus Host Disease
HES = Hydroxyethyl starch
HPCs = Hematopoietic Progenitor Cells
NCBP = National Cord Blood Program
RBCs = Red Blood Cells
TNCs = Total Nucleated Cells
TRM = Treatment Related Mortality
UCB = Umbilical Cord Blood

Application History: Complete BLA submitted on 28-Jan-2015

Cross-referenced files: N/A

Table of Contents

Introduction:

The product, HPC, Cord Blood, is manufactured by Puget Sound Blood Center Cord Blood Services. HPC, Cord Blood is prepared from voluntarily donated collections of umbilical CB taken from the umbilical cord and draining the fetal side of the placenta after the infant is delivered and the umbilical cord is cut into a collection bag containing (b) (4) . The aseptically collected units are transported under temperature-monitored conditions to the manufacturing site, the Puget Sound Blood Center. Units are evaluated by the Cord Blood Services laboratory for completeness of labeling and documentation, volume, cell counts, and viability of the products received.

Processing of qualified units from the collected whole CB into a plasma-reduced and RBC-reduced buffy coat product occurs in the environmentally monitored, controlled access processing laboratory. The buffy coat is produced using an (b) (4)

(b) (4) The final product contains HPCs in 10% DMSO cryoprotectant and 1% Dextran 40.

Proposed Mechanisms of Action:

The precise mechanisms of action are unknown. However, it is hypothesized that following intravenous administration the HPC, Cord Blood may migrate to the bone marrow, where the cells divide and mature, and are then released into the bloodstream, to restore blood counts and function (including immune function) of blood-borne cells of marrow origin. In subjects with inborn errors of metabolism, mature leukocytes generated from HPC, Cord Blood transplantation may synthesize the missing enzyme. The extent of disease correction depends on the disease and on the condition of the subject undergoing transplant.

Comment:

- The BLA submission did not include specific preclinical studies to support the purported mechanisms of action of HPC, Cord Blood in the proposed disease indications. Section 4.2 of the submission states that "HPC, Cord Blood transplantation had an unusual product history in that the episode of use occurred in a human sibling transplantation case in 1988 as described by Gluckman et al. in 1989. The success of that case led to further use in transplantation of HPC, Cord Blood. In 1996 successful use of unrelated, allogeneic HPC, Cord Blood transplantation was described by Kurtzberg et al. Data referenced in this application are from clinical studies."

For complete review of clinical data included in BLA submission, please refer to the clinical review memo. In addition to the BLA-cited articles by Gluckman et al. and Kurtzberg et al., this reviewer selected representative articles from the published literature that relate to the purported mechanisms of action of this product:

Gluckman E et al., Hematopoietic reconstitution in a patient with Fanconi's anemia by means of umbilical-cord blood from an HLA-identical sibling. New Eng J Med, 321 (17): 1174-1178, 1989

In this article, the authors reported that UCB from an HLA-identical sibling was transplanted into a boy with severe Fanconi's anemia. The patient received a cyclophosphamide and irradiation conditioning regimen, followed by infusion of 0.4×10^8 TNCs/kg. Cyclosporine was administered for prevention of GVHD. Engraftment of donor cells was demonstrated and the authors concluded that UCB can be an effective source of stem cells for hematopoietic reconstitution.

Kurtzberg J et al., Placental blood as a source of hematopoietic stem cells for transplantation into unrelated recipients. New Eng J Med, 335(3): 157-166, 1996
In this article, the authors reported that partially HLA mismatched placental blood from unrelated donors was transplanted in 25 patients (primarily children) with an age range of 0.8-23.5 years, with a variety of malignant and nonmalignant conditions between 1993 and 1995. These patients received placental blood from the unrelated donors (obtained from the Placental Blood Program, Duke University Medical Center), and were evaluated for hematologic and immunologic reconstitution and for GVHD. The patients received immunosuppressive agents post-transplant. Engraftment of the infused cells was documented in 23/25 transplant recipients. Hematopoietic reconstitution occurred by a median of 22 days (range of 14 - 37 days). Acute grade III GVHD occurred in 2/21 evaluable patients and another 2/21 patients had chronic GVHD. No patient developed acute grade IV GVHD. The *in vitro* proliferative T cell and B cell response to plant mitogens was detected at 53, 60, 95, 192, 380, and 820 days after transplantation. Natural killer cell function was normal in six patients tested at 2-3 months after transplantation. The overall 100-day survival rate among these patients was 64% and the overall event-free survival rate was 48%. The authors concluded that partially mismatched placental blood from unrelated donors is an alternative source of stem cells for hematopoietic reconstitution.

Laughlin MJ et al., Hematopoietic engraftment and survival in adult recipients of umbilical cord-blood from unrelated donors. N Eng J Med, 344(24): 1815-1822, 2001
The authors studied the ability of transplanted UCB to restore hematopoiesis in 68 adults with life-threatening hematologic disorders. Following intensive chemotherapy or total-body irradiation, transplants consisting of HLA-mismatched UCB obtained from the Placental Blood Program of New York Blood Center (57 units) and other blood banks (11 units) were administered. Endpoints assessed included hematologic reconstitution, the occurrence of acute and chronic GVHD, relapse, and event-free survival. A total of 48/68 patients (71%) received units that were mismatched for two or more HLA antigens. Of the 60 patients who survived 28 days or more after transplantation, 55/60 had neutrophil engraftment at a median of 27 days (range of 13-59 days). The neutrophil recovery correlated with the number of nucleated cells in the UCB before it was frozen. Severe acute GVHD (grade III or IV) occurred in 11/55 patients evaluated within l00 days after transplantation. Chronic GVHD developed in 12/38 patients who survived more than 100 days after transplantation. The median follow-up time for survivors was 22 months (range of 1l-5l months). As of the writing of this article, 19/68 (28%) patients remained alive, with 18/19 (95%) disease-free at 40 months after transplantation. The presence of a high number of CD34+ cells in the graft was associated with improved event-free survival ($P = 0.05$).

Wagner JE et al., Transplantation of unrelated donor umbilical cord blood in 102 patients with malignant and nonmalignant diseases: influence of CD34 cell dose and HLA disparity on treatment-related mortality and survival. Blood, 100: 1611-1618, 2002
The authors used cryopreserved unrelated donor UCB (obtained from the New York Blood Center, St. Louis Cord Blood Bank, Netcord, Milano, Dusseldorf, and Firenze Blood Center) in an attempt to reduce the risk of GVHD and TRM, and improve survival in patients with malignant (n = 65) and non-malignant (n = 37) diseases (median age of 7.4 years [range of 0.2-56 years]), such as AML, ALL, CML, various bone marrow failure syndromes, immune

deficiency, or various metabolic disorders, received transplants between 1994 and 2001. The UCB grafts contained a median of 2.8 x 10^5 CD34 cells. The patients received immunosuppressive agents post-transplant. Results from these patients at a median follow-up time of 2.7 years (range of 0.3-7.2 years) showed: 1) incidence of neutrophil engraftment of 0.88; 2) incidence of platelet engraftment of 0.65; and 3) incidence of severe acute and chronic GVHD of 0.11 and 0.10, respectively. At one and two years post-transplant, the incidence of TRM was 0.3 and 0.35, respectively, and the incidence of survival was 0.58 and 0.47, respectively. The rate of engraftment, TRM, and survival was associated with the CD34 cell dose (via Cox regression analyses).

Staba S et al., Cord blood transplants from unrelated donors in patients with Hurler's Syndrome. New Eng J Med, 350(19): 1960-1969, 2004

The authors report that between 1995 and 2002, following a myeloablative conditioning regimen, 20 children with Hurler's Syndrome received cryopreserved CB transplants from unrelated donors (source for CBU not specified, but most probably obtained from the Placental Blood Program, Duke University Medical Center). The donors had normal α-L-iduronidase activity and were discordant for up to three of six HLA loci. The patients received immunosuppressive agents for up to 9 months post-transplant. Neutrophil and platelet engraftment occurred at a median of 24 days (range of 10-39 days) after transplantation and the CD4+ cell counts progressively increased. A total of 25% (5/20) of the patients had grade II or grade III acute GVHD at a median of 21 days (range of 8-35 days) post-transplant; none had extensive chronic GVHD. Per the article, at approximately one year after the last transplant, a total of 17/20 children were alive, (a median of 905 days [range of 333-2817 days]). These children displayed complete donor chimerism and normal α-L-iduronidase activity in peripheral blood samples. The authors conclude that CB transplantation improved the neurocognitive performance and decreased some somatic features of this disease.

Escolar ML et al., Transplantation of Umbilical-Cord Blood in Babies with Infantile Krabbe's Disease. N Engl J Med, 2069-2081, 2005

The authors transplanted UCB from unrelated donors (source: National Marrow Donor Program and New York Blood Center) in 11 newborn patients before the development of infantile Krabbe's disease symptoms occurred (4 boys and 7 girls; 12-44 days old) and in 14 newborn patients after the development of disease symptoms (8 boys and 6 girls; 142-352 days old). Both the asymptomatic and the symptomatic infants were transplanted after myeloablative chemotherapy. Outcomes among these newborns were compared to each other and to the outcomes in a cohort of affected children that were not transplanted. Engraftment (neutrophil and platelet), survival, and neurodevelopmental function were evaluated longitudinally for four months to six years.

The results showed that among the asymptomatic infants (median follow-up of 3.0 years), the rates of donor cell engraftment and survival were 100%. Among the symptomatic infants (median follow-up of 3.4 years) the rate of donor cell engraftment and survival was 100% and 43%, respectively. Restoration of normal blood galactocerebrosidase levels was observed in all surviving infants. Infants who received UCB before the development of symptoms showed progressive central myelination and continued gains in developmental skills, and while most had age-appropriate cognitive function and receptive language skills, a few had mild-to-moderate

delays in expressive language and mild-to-severe delays in gross motor function. Infants who received UCB after the onset of symptoms had minimal neurologic improvement.

Ruggeri A et al. Umbilical cord blood transplantation for children with Thalassemia and sickle cell disease. Biol Blood Marrow Transplant, 1-9, 2011

In this article the authors reported the efficacy of unrelated CB transplantation in children with thalassemia (n = 35) and sickle cell disease (SCD; n = 16), using data reported to three registries (National Cord Blood Program [NCBP], New York Blood Center, and Center for International Blood and Marrow Transplantation Registry). All children received a single unmanipulated CB unit. Transplant conditioning was myeloablative (n = 39) or reduced intensity (n = 12). Neutrophil recovery was measured for three consecutive days, with donor engraftment determined by a chimerism assay. The results showed neutrophil recovery with complete donor chimerism in 24/51 (47%; n = 15 thalassemia, n = 9 SCD) patients and the median time of neutrophil recovery was 22 days (range of 10-62 days). None of the patients developed secondary graft failure. The median time to platelet recovery was 40 days (range of 15-127 days). Eleven patients developed grade II-IV acute GVHD and 10 patients developed chronic GVHD. Overall survival and disease-free survival were 62% and 21% respectively, for thalassemia patients and 94% and 50% respectively, for SCD patients. The engraftment rate (P = 0.05) and disease-free survival (P =0.01) were higher with administration of $>5 \times 10^7$ TNCs/kg. Primary graft failure occurred in 20 [out of 35] (fatal in 5/7 cases) patients with thalassemia and 7 [out of 16] patients with SCD. The authors conclude that only CB units containing an expected infused dose of $>5 \times 10^7$ TNCs/kg should be transplanted in patients with hemoglobinopathies.

Comment:

- Section 12.1 of the Package Insert (PI) provided in the submission titled, "Mechanism of Action" reflects the published data. Below is the proposed wording for this section as of the writing of this review:

  Hematopoietic stem/progenitor cells from HPC, Cord Blood migrate into the bone marrow after infusion where they divide and mature. The mature cells are released into the bloodstream, where some circulate and others migrate to tissue sites, partially or fully restoring blood counts and function, including immune function, of blood-borne cells of marrow origin. [See Clinical Studies (14)].

  In patients with enzymatic abnormalities due to certain severe types of metabolic storage disorders, mature leukocytes resulting from HPC, Cord Blood transplantation may synthesize enzymes that may be able to circulate and improve cellular functions of some native tissues. However, the precise mechanism of action is unknown.

Preclinical Studies:

Biocompatibility Studies

No biocompatibility or extractables and leachables testing of the storage bags were conducted by the sponsor. HPC, Cord Blood is composed of cells, and the device components used to generate

this biological product (i.e., the collection, processing, and cryopreservation of the cells) are approved/cleared by the FDA.

Proof-of-Concept (POC) and Toxicology Studies

No preclinical POC studies were conducted with the HPC, Cord Blood product. Toxicology studies as described in the International Conference on Harmonisation (ICH) Safety ('S') guidelines, consisting of pharmacokinetics, acute toxicology, chronic toxicology, genotoxicity, carcinogenicity, reproductive and developmental toxicity, safety pharmacology, and immunotoxicity (as described at http://www.ich.org/products/guidelines/safety/article/safety-guidelines.html) were not conducted by the sponsor due to the previous human experience with HPC, Cord Blood.

HPC, Cold Blood contains DMSO (C_2H_6OS; 10%). Per Regan et al., the maximum recommended dose of DMSO is 1 g/kg. This author also stated that the transplantation experience has shown that the toxicity of DMSO in the doses delivered by HPC products is generally minimal and transient.[1] When 20% DMSO-saline was administered via the tail vein in healthy (b) (4) rats (250-300 gm), hemolysis, leading to blood in the urine, occurred at 1 hour post-injection. No hemolysis was observed when 20% DMSO-saline was injected into the jugular vein of the rats. This difference was attributed to the rapid dilution of DMSO by the relatively higher blood flow in the jugular vein compared to that in the tail vein.[2]

Comment:

- The worst-case amount of DMSO that can be administered with one unit of HPC, Cord Blood is 10% (unwashed). The residual amount of DMSO in a single washed HPC, Cord Blood was not provided. Please refer to the clinical review for a discussion of the potential toxicities following exposure to DMSO.

Reproductive/Developmental Toxicity:
Following intraperitoneal injections of 5 to 12 g/kg of 50% DMSO on gestation days 6-12, 7/100 (7%) mouse fetuses obtained near or at term were deformed and 11/729 (1.5%) rat fetuses were deformed. Malformations noted consisted of anencephalia, microphalia, celosomia, edema, and limb, jaw, and/or tailbud deformities. Following intraperitoneal injection of 2.5-15 g/kg of 100% DMSO in hamsters on gestation days 6-14, 25% embryolethality was observed for dams given 15 g/kg, with exencephaly and anencephaly in 100% of the surviving fetuses.

Comment:

- Section 8.1 of the PI provided in the submission titled, 'Pregnancy' currently states:

  Pregnancy Category C. Animal reproduction studies have not been conducted with HPC, Cord Blood. It is not known whether HPC, Cord Blood can cause fetal harm when

[1] Regan DM et al., Comparison of cord blood thawing methods on cell recovery, potency, and infusion. Transfusion, 50:2670-2675, 2010.
[2] Fung S-Y, Oyaizu T, Yang H, Yuan Y, Han B, Keshavjee S and Liu M. The potential of nanoscale combinations of self-assembling peptides and amino acids of the Src tyrosine kinase inhibitor in acute lung therapy. Biomaterials 32: 4000-4008, 2011.

administered to a pregnant woman or can effect reproductive capacity. There are no adequate and well-controlled studies in pregnant women. HPC, Cord Blood should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

On December 03, 2014, the FDA issued a final rule regarding the labeling information that must be contained in the pregnancy and lactation section of the product label. [3] Thus, the sponsor will need to revise this section of the label. As of the writing of this review, recommended wording is as follows:

8.1. Pregnancy

Risk Summary

There are no data with HPC, Cord Blood use in pregnant women to inform a product-associated risk. Animal reproduction studies have not been conducted with HPC, Cord Blood. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

8.2 Lactation

Risk Summary

There is no information regarding the presence of HPC, Cord Blood in human milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for HPC, Cord Blood and any potential adverse effects on the breastfed infant from HPC, Cord Blood or from the underlying maternal condition.

As previously noted, HPC, Cord Blood also contains 1% Dextran 40. Please refer to the clinical review for the potential toxicities following exposure to this agent.

CONCLUSION

All device components used to prepare this product, HPC, Cord Blood, have been previously cleared or exempted by FDA. The anticoagulant used to prepare HPC, Cord Blood, is approved by FDA. No additional preclinical testing with HPC, Cord Blood was conducted by the sponsor.

[3] Known as the 'Pregnancy and Lactation Rule (PLLR), at:
http://www.fda.gov/biologicsbloodvaccines/guidancecomplianceregulatoryinformation/actsrulesregulations/ucm445102.htm.
FDA has also issued a draft guidance associated with this rule: *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format: Guidance for Industry* (December 2014), at:
http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm065010.htm

Key Words/Terms

(b) (4) ; HPC, Cord Blood; CB; UCB; DMSO;, Dextran 40; transplantation; toxicology; biocompatibility; reproductive/developmental toxicity